UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/241,653	02/02/99	WAGNER H	C1041/7002-H

HM12/0103

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EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	16

DATE MAILED: 01/03/01

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/241,653	Wagner et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- [X] Responsive to communication(s) filed on 10/03/00.
- [X] This action is **FINAL.**
- [ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- [X] Claim(s) 1-77 is/are pending in the application.
  - Of the above claim(s) _____ is/are withdrawn from consideration.
- [ ] Claim(s) _____ is/are allowed.
- [X] Claim(s) 1-77 is/are rejected.
- [ ] Claim(s) _____ is/are objected to.
- [ ] Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- [ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [ ] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- [ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
  - [ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
  - [ ] received.
  - [ ] received in Application No. (Series Code/Serial Number) _____.
  - [ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

- [X] Information Disclosure Statement(s), PTO-1449, Paper No(s). 15
- [X] Notice of References Cited, PTO-892
- [ ] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Interview Summary, PTO-413
- [ ] Notice of Informal Patent Application, PTO-152
- [ ] Other _____

Office Action Summary

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Old claims 1-65 and new claims 66-77 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of certain oligonucleotides in whole organisms for specific functions, does not reasonably provide enablement for the scope of such oligonucleotides for the functions broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the previous Official Action on the Merits mailed 03/30/00.

Applicant's arguments filed 10/03/00 have been fully considered but they are not persuasive.

Old claims 1-65 are drawn broadly to (1) methods for inducing an antigen-specific immune response comprising administering to a subject a CpG oligonucleotide wherein the CpG oligonucleotide includes at least 8 nucleotides, and exposing the subject to an antigen at least 3 days after the CpG oligonucleotide is administered to the subject to produce an antigen-specific immune response; (2) methods for increasing platelet counts in a subject having

thrombocytopenia, comprising: administering to a subject having (non-chemotherapeutic induced) thrombocytopenia a CpG oligonucleotide wherein the CpG oligonucleotide includes at least 8 nucleotides, in an amount effective to increase platelet counts in the subject; (3) methods of treating a subject at risk of developing thrombocytopenia comprising: administration to a subject at risk of developing thrombocytopenia a CpG oligonucleotide wherein the CpG oligonucleotide includes at least 8 nucleotides, in an amount effective to prevent a decrease in platelet counts ordinarily expected under platelet-depleting conditions in the subject when the subject is exposed to platelet-depleting conditions; and (4) methods for treating anemia, comprising: administering to a subject having anemia a CpG oligonucleotide wherein the CpG oligonucleotide includes at least 8 nucleotides, in an amount effective to induce erythropoiesis in the subject.

New claims 66-77 are drawn to methods for inducing an antigen-specific immune response, comprising: administering to a nonhuman vertebrate a CpG oligonucleotide, wherein the CpG oligonucleotide includes at least 8 nucleotides, and exposing the nonhuman vertebrate to an antigen at least 3 days after the CpG oligonucleotide is administered to the nonhuman vertebrate to produce an antigen-specific immune response. These new claims are held rejected for the same reasons of record as set forth in the previous Official Action mailed 03/30/00.

Applicants traverse the rejection first on the grounds that "Examiner appears to have based the rejection on the ground that the application does not teach one skilled in the art how to make and use the optimal oligonucleotide. However, enablement of the invention is independent of making and using the optimal oligonucleotide." Examiner agrees that the enablement of the

invention is independent of making and using the optimal oligonucleotide and the focus of the prior rejection was not to make that point. Instead, the scope of enablement rejection made focuses on the unpredictability known in the art for the scope of the invention as broadly claimed. The two primary issues are the lack of correlation and guidance in the art for design and administration of any such CpG oligonucleotide as broadly claimed to any subject for the functions claimed. Based on this unpredictability, one skilled in the art would not have been able to make and use the scope of oligonucleotides claimed (any CpG containing oligonucleotide greater than 8 nucleotides in length) for the functions claimed. This assertion does not characterize the lack of enablement as an issue of "optimization" of the claimed oligonucleotides.

Applicants further traverse the rejection by arguing that one skilled in the art could make and use the invention by making all combinations of the at least 8 nucleotides having the CpG oligonucleotide as claimed without undue experimentation. While examiner agrees that making all possible combinations of the 8 nucleotide sequence would not constitute undue experimentation in itself, several unpredictable factors exist for the functionality of said sequences as well as any other longer oligonucleotide as claimed. Specifically, the unpredictability in the art stems from the lack of correlation in the art between administration of any such CpG oligonucleotide and the claimed functions in any subject as claimed. Although one skilled in the art can envision making all combinations of the 8 nucleotide sequence, can one of skill in the art correlate administration of all these sequences to any organism for the therapeutic functions

claimed? Examiner argues that one skilled in the art, based on the unpredictability in the art cited, would not be able to make and use any such CpG containing oligonucleotide as broadly claimed.

Applicant further argues that the Zhao reference "in fact serves to support the argument that the amount of experimentation is limited. This is so because the statement teaches that it is unnecessary to try randomly (or even non-randomly) selected sense and antisense sequences directed to any of an immense number of possible candidate target genes. Rather is necessary only to identify particular sequences containing an unmethylated CpG dinucleotide, e.g., selected from among the 16 possible sequences embraced by the formula 5' X1CGX2 3'. In response, Examiner disagrees with the assumption that Zhao supports the argument that the amount of experimentation is limited. Although the invention does not constitute the design of nucleic acid sequences to target specific gene sequences, the design of functional oligoncueotides administered for the functions claimed shares some common problems with administration of antisense to whole organisms. For instance, both embrace the unpredictable factors of (1) degradation of the nucleic acids, lack of stability in vivo, causing the need for high dosage levels leading to toxicity, (2) non-specific binding of oligonucleotides in whole organisms leading to toxicity, and (3) depending on routes of administration, high variability in the areas of the organism reached such that the functions, in this case the therapeutic functions, may be effected and maintained. These factors are highly variable in the art for administration of any nucleic acid composition as broadly claimed and thus support the assertion that one skilled in the art would necessarily practice undue experimentation to make and use the claimed oligonucleotides for the functions claimed.

In regards to the assertion that Krieg et al. merely teaches optimization of the invention, not dealing with the instant enablement, Examiner disagrees since the focus of the rejection was not to teach an inability to 'optimize' an oligonucleotide in the art. Krieg cites that in his case "optimal B cell activation requires a DNA motif..." does mean that the entire enablement question of the instant claims revolves around optimization of the instantly claimed oligonucleotides. Theoretically, the instant invention reads on any conceivable CpG containing nucleic acid anyway, so therefore no optimization would ever be needed. However, this is not the main issue. Instead, Krieg serves to support the idea that depending on what problem is to be solved, what function the claims are drawn to provide, depends on the efficacy of the claimed oligonucleotide administered. The art clearly teaches the variability expected from administering different sequences of oligonucleotides, at different concentrations, via different routes of administration, and the chemistry of the subject species. Thus to provide correlation such that one skilled in the art could make and use any conceivable CpG containing oligonucleotide would require undue experimentation since neither the specification nor the art provide sufficient guidance for design of specific constructs enabled in any whole organism as broadly claimed.

The specification as filed teaches a specific response in mice to administration of certain CpG containing oligonucleotides. Examiner maintains the argument that one skilled in the art would does not have guidance to correlate these results to an expectation of success of administering any such CpG oligonucleotide to any other species as broadly claimed. Note McCluskie et al. who teach the unpredictability in the art for administration of DNA vaccines to

different species. Thus although Crystal was cited previously to argue that unpredictability in the art for correlation between effects seen in mice and effects seen in humans, McCluskie et al. further support this unpredictability. As in the case of any nucleic acid based therapy (gene therapy, antisense, etc.), there are isolated examples in the art of therapeutic success. However, the overall state of the art at the time of invention and now, still retains a high level of unpredictability as argued above for correlation between success with one oligonucleotide and in one organism and any other similarly designed sequence.

Applicants arguments thus do not overcome a *prima facie* case of lack of enablement for the scope of the claimed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
January 2, 2001

REMY YUCEL, PH.D
PRIMARY EXAMINER